STIC-ILL

ND

From: Holleran, Anne
Sent: Tuesday, September 04, 2001 6:03 PM
To: STIC-ILL
Subject: refs. for 09/251,133

362375

Examiner: Anne Holleran
Art Unit: 1642; Rm 8E03
Phone: 308-8892
Date needed by: ASAP

Please send me copies of the following :

1. Chien, J. et al. Mol. and Cell. Endocrinology (2001) 181(1-2): 69-79
2. Chien, J. et al. Int. J. of Cancer (2001) 91(1): 46-54
3. Chien, J. et al. Oncogene (1999) 18(22): 3376-3382
4. Wong, E.C.C. et al. Proc. Amer. Assoc. for Cancer Res. (1997) 38: 288
5. Rayford, W. et al. Prostate (1997) 30(3): 160-166
6. Xue-Zhang, Q. et al. Endocrine (1995) 3(6): 445-451
7. Shah, G.V. et al. Endocrinology (1994) 134(2): 596-602
8. Rayford, W. et al. J. of Urology (1994) 151(5 suppl): 490A
9. Rayford, W.et al. J. of Urology (1993) 149(4 suppl): 479A
10. Shah, G.V. et al. Prostate (N.Y.) (1992) 21(2): 87-97
11. Sagol, O. et al. Annals of Medical Sciences (1999) 8(1): 14-21
12. Sussenot, O. et al. Prostate (1998) 36(suppl. 8): 43-51
13. Hanna, F.W. et al. J. Endocrinol. (1997) 152(2): 275-281
14. Sim, S.J. et al. Annals of Clinical and Laboratory Science (1996) 26(6): 487-495
15. Watanabe, K. et al. Fukushim J. Medical Science (1995) 41(2): 141-152
16. Esik, O. et al. European J. Gynaecological Oncology (1994) 15(3): 211-216

Calcitonin-secreting ovarian strumal carcinoid

O. ÉSIK - G. NÉMETH - K. SZEPESHÁZI (*)

Summary: A 3-mm strumal carcinoid was found incidentally in a mature ovarian cystic teratoma of a 38-year-old woman followed up for more than 9 years. Although the thyroid component disclosed a typical normal light microscopic appearance, no thyroglobulin and thyroxine were detected immunohistochemically. Immunoreactive calcitonin was demonstrated within the tumour cells. The close relationship between functionally imperfect thyroid tissue and a neuroendocrine marker-secreting tumour seems to be concordant with the theory of the existence of a pluripotential stem cell capable of differentiating multidirectionally.

Key words: Ovary; Strumal Carcinoid; Calcitonin; Thyroglobulin; Thyroxine.

INTRODUCTION

Thyroid tissue has been reported in from 7 to 13 per cent of benign ovarian cystic teratomas ([1, 2]). If it is a major constituent, the tumour is referred to as an ovarian struma. The tumorous transformation of an ovarian struma is a rather rare phenomenon. As the thyroid tissue has two components, an endodermal and a neuroectodermal one, both types of cancer may arise from an ovarian struma. The tumorous transformation of the neuroectodermal component is traditionally called carcinoid.

The ovarian strumal carcinoid was first described by Scully in 1970 ([14]). The sine qua non of this entity is an intimate mixture of thyroid tissue with carcinoid. Besides the characteristic light microscopic appearance, a final histopathological diagnosis demands immunohistochemical/ultrastructural studies. The former may reveal neuroectodermal peptide hormones, marker proteins or biogenic amines, while the latter may detect neurosecretory granules. The clinical course of the disease is generally benign.

One-hundred and thirteen cases of ovarian strumal carcinoid have been collected from the world literature ([1–22]). We report an additional case of a small calcitonin-secreting tumour which was diagnosed incidentally and followed up for more than 9 years.

CASE REPORT

The case history of this 38-year-old woman revealed unilateral subtotal thyroidectomy for struma nodosa colloides. The thyroid function had subsequently remained normal without the need for any medication.

A 5-cm enlargement of the right ovary was observed during routine gynaecological examinations over 13 years. Finally, in 1984 laparo-

From the Department of Radiotherapy,
National Institute of Oncology
(*) Department of Pathology,
Ferenc Jahn Municipal Hospital,
Budapest (Hungary)

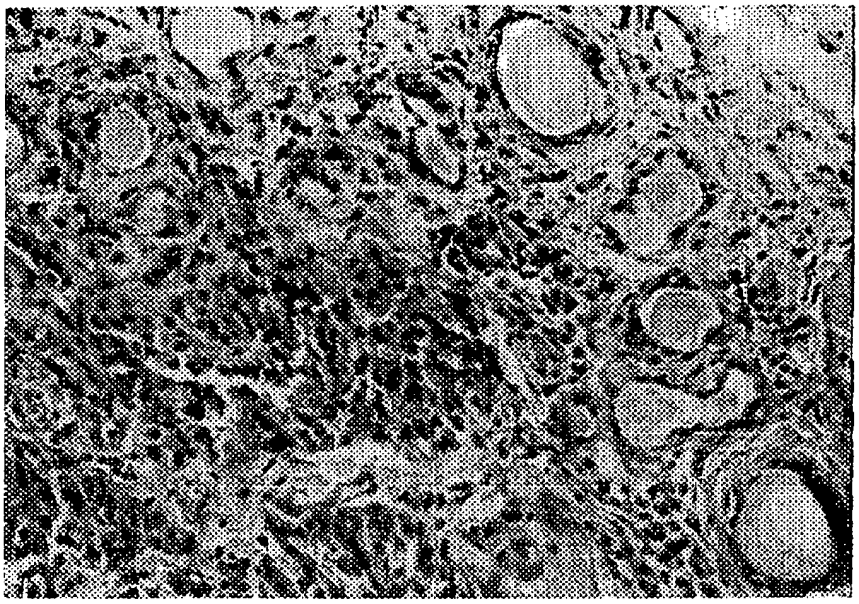

Fig. 1. — Thyroid follicles are overgrown by epithelium-like tumour cells (HE ×300).

scopy was performed and a suspect tumour was detected. Right-sided salpingo-oophorectomy was carried out. Regular menstruation did not recur following the surgical intervention.

Macroscopically a normal ovary was found attached to a cystic structure with maximum diameter of 4 cm. Following transsection of the preparation, two cavities appeared, containing yellow-gray jelly-like substance with a few hairs.

Besides normal ovarian tissue, the light microscopy disclosed a mature cystic teratoma with the following tissues: squamous epithelium, sebaceous glands, hair follicles, bronchial epithelium, smooth muscle, bone trabeculae, islands of chondrocytes, mucus glands, brain tissue and peripheral nerve ganglion.

In the vicinity of the bronchial wall, a 3-mm focus of thyroid tissue with a normal light microscopic appearance was seen; it merged imperceptibly with other cell types (Fig. 1). These epithelium-like, monomorphic cells with granular cytoplasm and round nuclei were arranged in trabeculae and overgrew the marginal thyroid follicles. No mitoses were observed. Silver impregnation techniques (Fontana-Masson, Grimelius) failed to demonstrate argentaffinity or argyrophilia. Amyloid was negatively stained with Congo red under polarizing microscope.

On the basis of the light microscopic morphologic features, the histopathological diagnosis of a medullary thyroid carcinoma arising from ovarian thyroid tissue was established in 1984. However, this was not confirmed by immunohistochemical or electron microscopic examinations at that time.

The patient was referred to the radiotherapy department for consultation on postoperative treatment. Right-sided pelvic irradiation was decided on and delivered by a telecobalt unit with a midplane dose of 36 Gy.

During the past 9-year follow-up, physical examinations have failed to detect recurrence, and there has been no sign of tumour development in the contralateral ovary either. Recent abdominal CT and US results were also negative.

In 1992 the original blocks were submitted for immunohistochemical studies. Calcitonin secretion was investigated by immunoperoxidase techniques with polyclonal anticalcitonin raised in rabbit (DAKO, Copenhagen, Denmark). The appearance of brownish pigment in the cytoplasm of the tumour cells indicates a positive reaction (Figs. 2 *a*, *b*). This calcitonin positivity was detectable in the transitional zone between the thyroid tissue and the neuroectodermal component and in tumour cells situated in the interfollicular space. It was missing, however, in the epithelial lining of the follicles.

In view of this immunohistochemical finding, serum calcitonin levels were checked (RIA-mat kit, Byk Sangtec). The two tests performed so far have revealed normal (< 7.8 pg/ml) values.

The presence of thyroglobulin and thyroxine was investigated with polyclonal antithyroglobu-

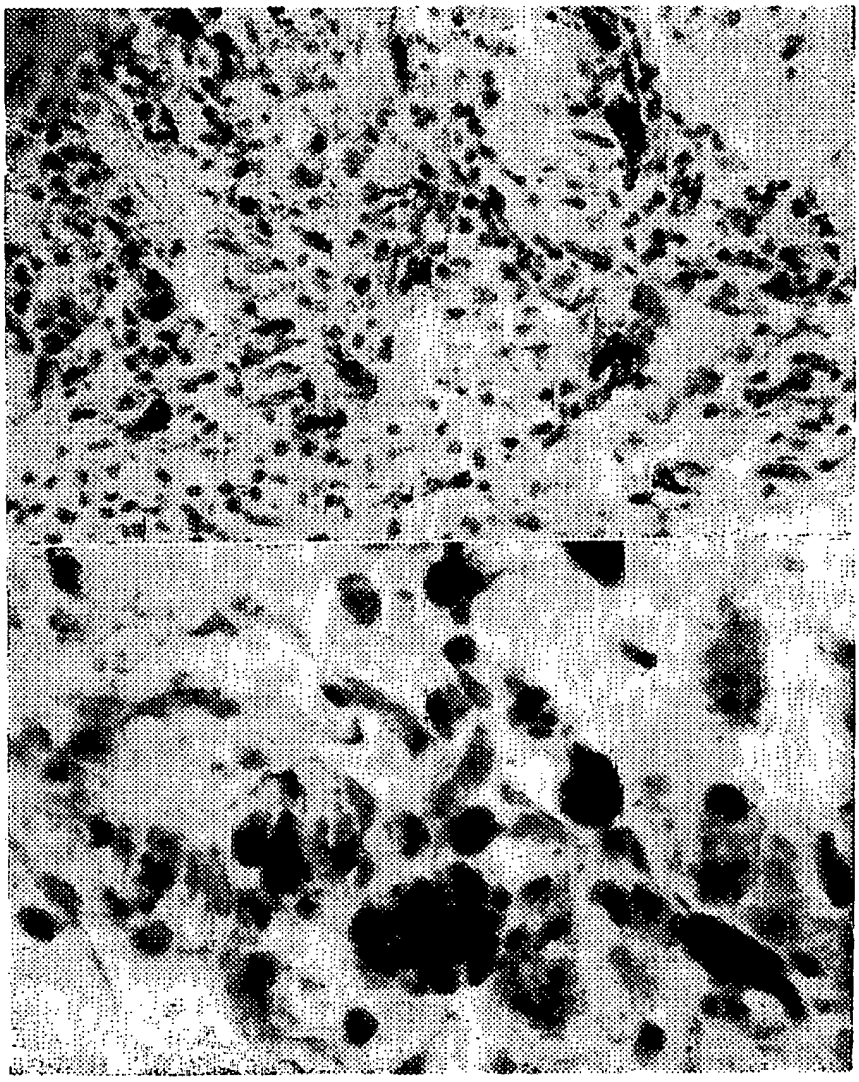

Fig. 2. — Tumour cells give a positive reaction with anticalcitonin (immunoperoxidase). *a*) ×300; *b*) ×650.

line (DAKO, Copenhagen, Denmark) and antithyroxine (Cambridge Research Laboratory, Cambridge, USA) raised in rabbit. The immunoperoxidase reactions in the thyroid tissue and the tumour cells were negative.

DISCUSSION

With the exception of the tumour size, the clinical history of our patient has been a typical one. By definition, an ovarian struma is a larger tumour: only three cases with a maximum diameter < 1 cm have been reported ([12, 18]). The finding of an exceptionally small tumour in our patient may relate to the thorough preparation of the specimen and even to good fortune.

The majority of subjects with ovarian strumal carcinoid are postmenopausal. Our patient might be of perimenopausal

age, her menopause set in following right-sided salpingo-oophorectomy. This may be explained by the loss of the right ovarian function which had previously been dominant despite the existence of the tumour in it. Scattered irradiation to the preserved left ovary was certainly not so high as to cause the cessation of menstruation.

Struma carcinoid is always unilateral and comprises some part of another tumour [especially benign cystic teratomas, and sometimes other borderline/low-grade tumours ([12,18])] in 50-60% of the cases. In our patient, it was part of a mature teratoma.

The therapy of ovarian struma carcinoid is like that of other low-grade ovarian malignancies: in younger patients unilateral, and in older subjects bilateral salpingo-oophorectomy is the treatment of choice. Postoperative radio- or chemotherapy is seldom indicated. In our case, the use of radiotherapy likewise seemed unnecessary. The decision for irradiation stemmed in part from the lack of earlier personal experience, and in part from published accounts of the radiotherapeutic management of this tumour type ([8, 12]).

A close follow-up of these patients is mandatory, because there is a 10 per cent incidence of contralateral ovarian tumour development ([12, 16]). There was no such finding in our patient during the past 9 years, but a longer follow-up is needed.

A progressive clinical picture and dissemination are exceptionally rare events in ovarian struma carcinoid. Only two cases have been reported which show some kind of metastatization ([12, 22]). In one patient ([12]), however, the metastases were mainly endodermal in origin (adenocarcinoma) and the neuroectodermal elements were merely incidental. In our case, there has been no sign of dissemination so far, i.e. the histological marks of malignancy have not resulted in similar clinical consequences.

The histological diagnosis was established by light microscopic examination, using conventionally stained sections, as the two cell lines were clearly distinguished from each other. The ovarian thyroid tissue had a normal light microscopic appearance in our case, although others have reported struma colloids, benign and malignant tumours in it ([12, 14-16]).

Although the ribbon-like neuroectodermal cells were immediately identified, their origin was not-clear-cut in 1984 on the use of conventional methods, owing to the absence of argentaffinic and argyrophilic reactions, the non-occurence of silver impregnation and negative amyloid staining. The absence of argentaffinic and argyrophilic reactions, however, does not exclude a neuroectodermal origin: this is the case in other neuroectodermal tumours as well. The lack of silver impregnation may merely indicate a relatively low number of secretory granules responsible for the reaction. The negative amyloid reaction does not disclose the origin of the tumour either, since its presence is not specific for calcitonin-secreting tumours or even strumal carcinoids. The presence of non-immune amyloid in strumal carcinoid has been demonstrated only four times ([1, 2, 4, 12]).

The accuracy of the earlier light microscopic finding was confirmed 9 years later by immunohistochemical studies of pathognomic significance. Although several immunoreactive peptides [glucagon/ enteroglucagon, somatostatin, pancreatic polypeptide, prostatic acid phosphatase, chromogranin, etc. ([3, 5, 9, 13, 16-18])] have been identified in 42-50% ([16, 17]) of the neuroectodermally programmed strumal carcinoid cells, calcitonin secretion has been reported in only 11 cases ([2, 4, 7, 9, 12, 13, 17, 18, 21]). It was a lucky event that our case stained positively for calcitonin, because it was the only peptide tested. The choice for it was strongly influenced by the original description of medullary carcinoma.

In view of the presence of calcitonin in cancer cells, serum determination of this marker protein could be used as a subsequent indicator for tumour recurrence.

To prove the origin of the other tissue was more complicated. Although light microscopy disclosed a typical thyroid tissue-like appearance, no thyroglobulin and thyroxine were detected. A strong argument confirming the dissimilarity of thyroid-like and neuroectodermal elements may be the absence of calcitonin positivity in the epithelial lining of the follicles.

In the majority of publications the origin of the thyroid tissue is confirmed by the presence of either thyroglobulin or thyroxine ([3,5,7,9,15,16,18-21]). In several cases, however, confirmation of the thyroid component seems problematic. The cause of this phenomenon is multifactorial. Many investigators did not perform the reactions at all, while some did, but failed ([13]). The possibility of technical error must be considered, together with the fact that these tumour cells may be functionally imperfect, losing features related to iodine metabolism.

The histogenesis of strumal carcinoid is a matter of controversy. Most authors prefer the monophyletic theory, i.e. they consider that the thyroid tissue and the neuroectodermal elements arise from the same primordium ([3, 5, 9, 12, 14, 16, 18, 19, 21]). All other theories presume that the two components have different origins. The possible kinship of ovarian strumal carcinoid to medullary carcinoma of the thyroid, has been extensively discussed and especially questioned on the basis of the observed lack of calcitonin secretion, amyloid deposition and dissemination in strumal carcinoid.

Whatever the origin and relations of this rare and interesting tumour, it is expected to contribute to our present knowledge on tumour histogenesis, development and spreading.

REFERENCES

1) Arhelger R. B., Kelly B.: "Strumal carcinoid. Report of a case with electron microscopical observations". *Arch. Pathol.*, 1974, *97*, 323.
2) Blaustein A.: "Calcitonin secreting struma-carcinoid tumor of the ovary". *Hum. Pathol.*, 1979, *10*, 222.
3) Czerwenka K. F., Schön H. J., Böck P.: "Immunochemical and ultrastructural studies of an ovarian strumal carcinoid". *Wien. Klin. Wochenschr.*, 1990, *102*, 687.
4) Dayal Y., Tashjian A. H., Wolfe H. J.: "Immunocytochemical localization of calcitonin-producing cells in a strumal carcinoid with amyloid stroma". *Cancer*, 1979, *43*, 1331.
5) De Maurizi M., Bondi A., Betts C. M., Eusebi V.: "Strumal carcinoid of the ovary: an immunohistochemical and electron microscopic study". *Tumori*, 1983, *69*, 261.
6) Dikman S. H., Toker C.: "Strumal carcinoid of the ovary with masculinization". *Cancer*, 1971, *27*, 925,
7) Greco M. A., LiVolsi V. A., Pertschuk L. P., Bigelow B.: "Strumal carcinoid of the ovary. An analysis of its components". *Cancer*, 1979, *43*, 1380.
8) Hart W. R., Regezi J. A.: "Strumal carcinoid of the ovary. Ultrastructural observations and long-term follow-up study". *Am. J. Clin. Pathol.*, 1978, *69*, 356.
9) Kimura N., Sasano N., Namiki T.: "Evidence of hybrid cell of thyroid follicular cell and carcinoid cell in strumal carcinoid". *Int. J. Gynecol. Pathol.*, 1986, *5*, 269.
10) Livnat E. J., Scommegna A., Recant W., Jao W.: "Ultrastructural observations of the so-called strumal carcinoid of the ovary". *Arch. Pathol. Lab. Med.*, 1977, *101*, 585.
11) Ranchod M., Kempson R. L., Dorgeloh J. R.: "Strumal carcinoid of the ovary". *Cancer*, 1976, *37*, 1913.
12) Robboy S. J., Scully R. E.: "Strumal carcinoid of the ovary: an analysis of 50 cases of a distinctive tumor composed of thyroid tissue and carcinoid". *Cancer*, 1980, *46*, 2019.
13) Sakura H., Hamada Y., Tsuruta S., Okamoto K., Nakamura S.: "Large glucagon-like immunoreactivity in a primary ovarian carcinoid". *Cancer*, 1985, *55*, 1001.
14) Scully R. E.: "Recent progress in ovarian cancer". *Hum. Pathol.*, 1970, *1*, 73.
15) Senterman M. K., Cassidy P. N., Fenoglio C. M., Ferfenczy A.: "Histology, ultrastructure, and immunohistochemistry of strumal carcinoid: a case report". *Int. J. Gynecol. Pathol.*, 1984, *3*, 232.

16) Snyder R. R., Tavassoli F. A.: "Ovarian strumal carcinoid: immunohistochemical, ultrastructural, and clinicopathologic observations". *Int. J. Gynecol. Pathol.*, 1986, *5*, 187.
17) Sporrong B., Falkmer S., Robboy S. J., Alumets J., Hakanson R., Ljundberg O., Sundler F.: Neurohormonal peptides in ovarian carcinoids: an immunohistochemical study of 81 primary carcinoids and of intraovarian metastases from six midgut carcinoids and of intraovarian metastases from six midgut carcinoids". *Cancer*, 1982, *49*, 68.
18) Stagno P. A., Petras R. E., Hart W. R.: "Strumal carcinoids of the ovary. An immunohistologic and ultrastructural study". *Arch. Pathol. Lab. Med.*, 1987, *111*, 440.
19) Takubo K., Yasui H., Toi K.: "Strumal carcinoid of the ovary. A case report". *Acta Pathol. Jpn.*, 1986, *36*, 765.
20) Tsubura A., Sasaki M.: "Strumal carcinoid of the ovary. Ultrastructural and immuhistochemical study". *Acta Pathol. Jpn.*, 1986, *36*, 1383.
21) Ulbright T. M., Roth L. M., Ehrlich C. E.: "Ovarian strumal carcinoid. An immunocytochemical and ultrastructural study of two cases". *Am. J. Clin. Pathol.*, 1982, *77*, 622.
22) Woodruff J. D., Rauh J. T., Markley R. L.: "Ovarian struma". *Obstet. Gynec.*, 1966, *27*, 194.

Address reprint requests to:
O. ÉSIK
Department of Radiotherapy
National Institute of Oncology
H-1122,. Budapest XII, Ráth György u. 7-9
Hungary